The rationale and design of the Surgical Treatment for Ischemic Heart Failure (STICH) trial

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Objectives: The rationale and design of the Surgical Treatment for Ischemic Heart Failure trial is described. Before the Surgical Treatment for Ischemic Heart Failure trial, less than 1000 patients with ischemic cardiomyopathy had been studied in randomized comparisons of medical therapy versus coronary artery bypass grafting. Trial data reflect how these therapies were delivered more than 20 years ago and do not indicate the relative benefits of medical therapy versus coronary artery bypass grafting in contemporary practice.

Methods: Randomization of consenting patients with heart failure, left ventricular ejection fraction of 0.35 or less, and coronary artery disease is based on whether patients are judged by attending physicians to be candidates only for coronary artery bypass grafting or can be treated with medical therapy without coronary artery bypass grafting. Patients eligible for surgical ventricular reconstruction because of significant anterior wall akinesis or dyskinesis but ineligible for medical therapy are randomly assigned to coronary artery bypass grafting with or without surgical ventricular reconstruction. Patients eligible for medical therapy are randomly assigned between medical therapy only and medical therapy with coronary artery bypass grafting. Patients eligible for all 3 are randomly assigned evenly to medical therapy only, medical therapy and coronary artery bypass grafting, or medical therapy and coronary artery bypass grafting and surgical ventricular reconstruction. Major substudies will examine quality of life, cost-effectiveness, changes in left ventricular volumes, effect of myocardial viability, selected biomarkers, and selected polymorphisms on treatment differences.

Results: Enrollment is now complete in both STICH hypotheses. Follow-up will continue until sufficient end points are available to address both hypotheses with at least 90% power. The primary outcome of hypothesis 2 is expected to be reported in 2009. The primary outcome of hypothesis 1 is expected to be reported in 2011.

Conclusions: The Surgical Treatment for Ischemic Heart Failure trial is a National Heart, Lung, and Blood Institute–funded multicenter international randomized trial addressing 2 specific primary hypotheses: (1) coronary artery bypass grafting with intensive medical therapy improves long-term survival compared with survival with medical therapy alone, and (2) in patients with anterior left ventricular dysfunction, surgical ventricular reconstruction to a more normal left ventricular size plus coronary artery bypass grafting improves survival free of subsequent hospitalization for cardiac cause when compared with that with coronary artery bypass grafting alone.

The revascularization of patients with coronary artery disease (CAD) with left ventricular (LV) systolic dysfunction (SD) and symptomatic heart failure (HF) has been the subject of much debate and surprisingly little research over the past 30 years.[1,2] Our current understanding of how best to treat these patients stems from

Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CAD = coronary artery disease
CASS = Coronary Artery Surgery Study
EF = ejection fraction
H1 = hypothesis 1
H2 = hypothesis 2
HF = heart failure
LV = left ventricular
MED = medical therapy
NHLBI = National Heart, Lung, and Blood Institute
PCI = percutaneous coronary intervention
SD = systolic dysfunction
SVR = surgical ventricular reconstruction

subset analyses of the coronary artery bypass grafting (CABG)–medicine clinical trials performed in the 1970s and early 1980s and analyses of large registries of patients from the same era.[3-7] Although such analyses have generally demonstrated that patients with more advanced CAD and more severe LV dysfunction derive larger benefit from CABG relative to medical therapy (MED), in practice both cardiologists and surgeons have substantial uncertainty about whether these projected benefits are counterbalanced by the increased early risks of the surgical approach.

In 2002, the National Heart, Lung, and Blood Institute (NHLBI) funded the Surgical Treatment for Ischemic Heart Failure (STICH) trial to address 2 pressing clinical and policy questions regarding the management of patients with HF with surgically revascularizable CAD and decreased LV function: (1) Is contemporary CABG surgery superior to contemporary medical/secondary prevention therapy in prolonging survival in these patients? (2) Among patients with significant anterior wall dysfunction, does the addition of surgical ventricular reconstruction (SVR) to CABG improve hospitalization-free survival?

Materials and Methods

Study Design

In the absence of definitive data on the value of CABG in high-risk patients with LVSD, wide diversity exists among providers about how to select patients. Moreover, many patients who might be CABG candidates also have dominant anterior akinesia or dyskinesia that might be reasonable to reconstruct surgically at the time of CABG.[8] Therefore the STICH trial was designed to let physicians first determine whether potential STICH patients were amenable to CABG after their routine clinical assessment. A threshold LV ejection fraction (EF) of 0.35 or less was established, with no lower limit set to preclude study entry. Physicians are encouraged to use any cardiac testing necessary to decide whether an individual patient is a candidate for CABG, SVR, or both. This philosophy encourages the use of standard practice to identify patients for whom responsible physicians are at equipoise about MED, CABG, and CABG with SVR and ensures that the STICH cohort has characteristics that now pose the greatest uncertainty in clinical decision making for patients with ischemic cardiomyopathy. Moreover, all information now commonly used by clinicians in deciding on surgical treatment for a subset of patients with ischemic cardiomyopathy will be available so that the value added by each component to the decision-making process can be evaluated (Table 1).

Subjects meeting the broad inclusion criteria of CAD amenable to CABG with an LVEF of 0.35 or less, without a specific exclusion, are segregated into 3 strata (A, B, and C) depending on investigator-determined suitability for continued MED alone and eligibility for SVR (Figure 1). Eligibility for MED alone is defined by the investigator but generally excludes patients with an intraluminal left main coronary artery stenosis of 50% or greater or severe disabling angina (Canadian Cardiovascular Society Class ≥III) unresponsive to nonsurgical interventions. Eligibility for SVR is defined as dominant LV akinesia or dyskinesia amenable to SVR. Stratum A subjects are defined as suitable for MED with or without CABG, and consenting patients are randomly assigned in a 1:1 ratio between MED alone or with CABG. Stratum B subjects, defined as eligible for all 3 treatment options, are randomly assigned 1:1:1 to either MED alone, MED with CABG, or MED with CABG and SVR. Subjects eligible for CABG with and without SVR are randomly assigned 1:1 in stratum C to either CABG or CABG with SVR. After stratum eligibility is established and informed consent is obtained, treatment allocation is made to a specific therapy based on an undisclosed permuted block randomization scheme.

Study Population

The STICH trial is designed to enroll at least 2000 men and women aged 18 years and older who have CAD amenable to revascularization and LVSD defined by a clinically determined LVEF of 0.35 or less. STICH trial entry criteria are summarized in Table 2. Patients awaiting a planned percutaneous coronary intervention (PCI) to treat symptomatic CAD within the next 30 days are not eligible, although previous PCI is not an exclusion. Although planned operative treatment of the aortic valve excludes potential candidates, the decision to pursue operative management of any other valves, specifically the mitral valve, is left to the discretion of responsible physicians and surgeons.

Baseline and follow-up studies. After obtaining informed consent, baseline demographics, physical examination, laboratory data, and medical details, including procedural history and details, are collected, and all patients undergo any remaining requisite baseline studies (Table E1). Patients eligible for MED alone enrolled into strata A and B undergo baseline radionuclide perfusion and viability imaging and a modified Bruce protocol exercise stress test, if they are able to exercise. SVR-eligible patients enrolled into strata B and C preferably undergo baseline cardiovascular magnetic resonance or gated single photon emission computed tomographic perfusion imaging with follow-up at 4 and 24 months to assess postoperative size, shape, and function.

All STICH subjects will undergo echocardiography and blood sampling for neurohormonal, cytokine, and genetic analyses; a detailed quality-of-life assessment; and a 6-minute walk test, if appropriate, based on subject status. These baseline studies are

TABLE 1. Major STICH hypotheses

Primary hypotheses

H1: Coronary revascularization hypothesis

- Improvement in myocardial perfusion by CABG combined with MED improves long-term survival compared with MED alone.

H2: LV restoration hypothesis

- In patients with dominant anterior wall LV akinesia or dyskinesia, LV shape and size optimization by SVR combined with CABG and MED improves long-term survival free of cardiac hospitalization compared with CABG and MED without SVR.

Major secondary hypotheses

- Presence and extent of dysfunctional but viable myocardium, as defined by radionuclide imaging, dobutamine stress echocardiography, or both, will identify patients with greatest survival advantage of MED and CABG compared with MED alone.
- Echocardiographic assessment of LV systolic and diastolic dysfunction, cardiac hemodynamics, and valvular regurgitation at baseline will define patient subgroups that derive substantial improvement or incur substantial risk in all-cause mortality if treated with MED and CABG compared with MED alone.
- Surgical intervention with CABG will lead to greater sustained improvements at 4 and 24 months in echocardiography-derived indices of LV systolic and diastolic dysfunction, hemodynamics, and valvular regurgitation when compared with MED alone.
- Assessment of myocardial ischemia at baseline by means of radionuclide perfusion imaging during rest and stress will identify patients with a survival benefit of MED and CABG compared with those treated with MED alone.
- MED and CABG with SVR will lead to more improvement in LV end-systolic volume index measured serially at baseline, 4 months, and 24 months compared with MED and CABG without SVR.
- CMR assessment of the baseline LV sphericity index will add independent prognostic information beyond LV end-systolic index, regardless of treatment assignment, and MED and CABG with SVR will lead to an improved LV sphericity index when compared with MED and CABG alone.
- Extent of neurohormonal and proinflammatory cytokine activation will identify the patient subgroup most likely to derive substantial survival benefit from MED and CABG with or without SVR compared with MED alone.
- Presence of a favorable genotype (eg, low ACE gene expression/high adenosine expression) will identify the patient subgroup most likely to have long-term improvement in cardiovascular morbidity and mortality.
- MED and CABG will lead to incremental cost-effectiveness assessed as cost/life year added and cost/quality-adjusted life year added relative to MED alone.
- MED and CABG will lead to greater improvement in health-related quality of life

STICH, Surgical Treatment for Ischemic Heart Failure trial; *H1*, hypothesis 1; *CABG*, coronary artery bypass grafting; *MED*, medical therapy; *H2*, hypothesis 2; *LV*, left ventricular; *SVR*, surgical ventricular reconstruction; *ACE*, angiotensin-converting enzyme.

repeated in 4 months, with further repeat echocardiographic analysis performed at 24 months. Continuing assessment of quality of life and exercise capacity for all patients will occur at yearly intervals after randomization. Table E2 outlines STICH follow-up studies. Details of core laboratory testing protocols are available at www.stichtrial.org.

Medical therapy. The STICH Medical Therapy Committee is mandated to regularly review evidence and redefine optimal MED when necessary for all STICH subjects, regardless of randomization strata or treatment. Unless contraindicated, optimal MED includes angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or both; β-blocker; aldosterone antagonist; and antiplatelet agents adjusted to optimal doses within 30 days after randomization. Statin, diuretic, and digitalis use will be individualized to patient-specific indications. The use of implantable defibrillators is encouraged as part of MED and should be used in compliance with standard guidelines. A lead cardiologist at each site is responsible for ensuring high-quality MED for all patients, including those treated with surgical intervention.

Surgical therapy. Subjects randomly assigned to either CABG or CABG with SVR will receive the protocol-determined intervention no later than 14 days after randomization. CABG is performed by using at least 1 internal thoracic conduit, unless unavailable or inadequate. Use of cardiopulmonary bypass for CABG is left to the discretion of the surgeon. Patients with secondary mitral regurgitation judged to require mitral valve repair or replacement might undergo this procedure, although this is not mandated by protocol. The SVR typically occurs after CABG by means of any acceptable reconstruction method that consistently increases LVEF and decreases end-systolic volume. The general operative technique for SVR has been previously described.[8] Use of a sizing device to judge appropriate LV chamber size and the decision of whether and how to patch the LV closure site are left to the operating surgeon.

Before and during hypothesis 2 (H2) patient recruitment, multiple educational opportunities will be made available to cardiac surgeons to refine surgical decision making and operative techniques for patients undergoing SVR. A lead cardiac surgeon at each site is responsible for initially certifying that all STICH surgeons meet qualification standards set by the Surgical Therapy Committee and for maintaining a high quality of surgical care for the duration of the trial. The most experienced cardiac surgeons at each site are certified as eligible to operate on randomized patients. The minimum requirement for certification is evidence of 25 patients undergoing CABG with LVEFs of 0.40 or less who were operated on with 5% or lower mortality. Before cardiac surgeons are certified to perform SVR on a randomized patient, they are required to perform at least 5 SVR procedures without a perioperative death and demonstrate consistent LV volume reduction after the operation.

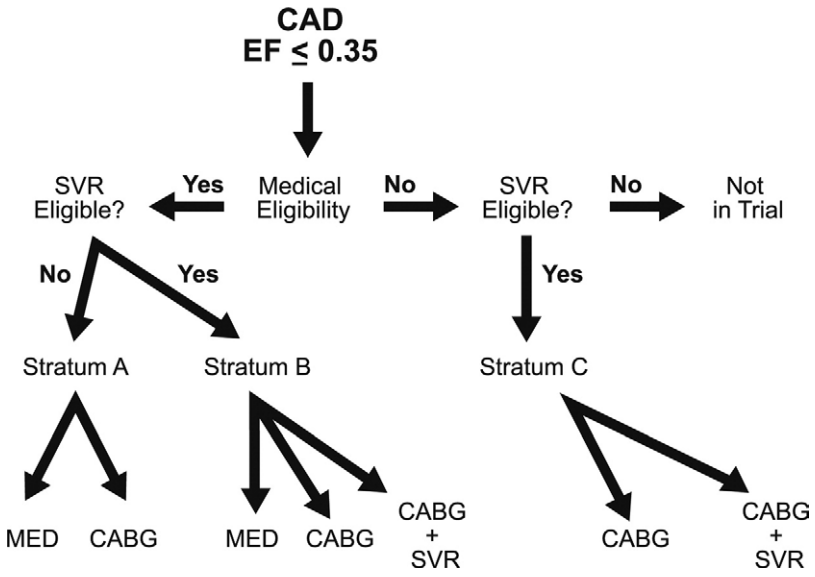

Figure 1. Surgical Treatment for Ischemic Heart Failure trial stratum and treatment assignment. *CAD*, Coronary artery disease; *EF*, ejection fraction; *SVR*, surgical ventricular reconstruction; *MED*, medial therapy; *CABG*, coronary artery bypass grafting.

Patient follow-up. The first follow-up for clinical status occurs at hospital discharge or at 30 days after randomization, whichever comes first. Participants are subsequently seen at 4-month intervals after randomization for the first year and no less than every 6 months after year 1. At these visits, interval assessments of HF and angina symptom status, current use of medications, and clinical end point data, including hospitalizations and procedures since the previous visit, are documented. Regardless of therapy received, all study participants are followed in this manner until study completion.

Statistical Issues

Hypothesis 1 power. All patients enrolled into stratum A and two thirds of patients enrolled into stratum B, those assigned to MED with or without CABG, comprise the hypothesis 1 (H1) study cohort. All-cause mortality is the primary end point of H1. H1 power estimates were based on an estimated 3-year mortality rate of 25% in the MED arm of the trial. This rate is slightly lower than the mortality observed in the control arm (no implantable cardioverter defibrillator implanted) of the ischemic cardiomyopathy cohort of the Sudden Cardiac Death in Heart Failure Trial.[9] Approximately 400 deaths are required to achieve 90% statistical power for detecting a treatment difference consisting of a 25% reduction in mortality with MED with CABG. These 400 deaths are projected to occur if at least 1000 H1 patients are followed for an average of 6.5 years or 1200 patients are followed for an average of 5.5 years.

Hypothesis 2 power. All patients randomly assigned to stratum C and the two thirds of patients entered into stratum B assigned to either CABG or CABG with SVR comprise the H2 study cohort. A composite end point of survival free of cardiac hospitalization was chosen for H2 because no data exist to suggest that adding SVR to CABG improves survival over CABG alone. Moreover, this composite end point has validity for patients who would be likely to consent to adding SVR to a planned CABG. The planned enrollment of 1000 patients into H2 provides a 90% power to detect a 20% reduction in mortality and cardiac hospitalization by the addition of SVR to CABG, assuming that the 3-year event rate for those treated with CABG alone is 45% or higher.

Treatment crossovers. Crossovers between MED to CABG or CABG and SVR are anticipated within the first year because of the dynamic nature of coronary disease and the potential for deteriorating symptoms unresponsive to standard MED and requiring symptomatic relief. Patients randomly assigned to CABG and SVR might also not receive SVR because of intraoperative decisions that maximize patient safety. PCI is not regarded as a treatment crossover but rather as downstream medical care associated with any of the treatment strategies tested in the STICH trial. The sample sizes for both H1 and H2 allow for treatment crossovers of as much as 20% without sacrificing power so long as the control event rates remain as projected.

Secondary end points. Secondary end points for both hypotheses include all-cause mortality at 30 days, cardiovascular mortality, survival free of HF hospitalization, survival free of subsequent revascularization, need for cardiac transplantation, need for an LV assist device, all-cause hospitalization, LV size, LV function, total health care costs, cost-effectiveness, and quality of life. Other important efficacy parameters that will be evaluated include fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, sudden death with or without resuscitation, survival free of PCI, and survival free of CABG.

Approach to data analysis. The primary efficacy analyses will be performed according to the principle of intention to treat; that is, patients will be analyzed (and end points attributed) according to the treatment arm to which they were randomly assigned, regardless of subsequent crossover or nonadherence to the assigned treatment. Statistical comparisons will be performed by using 2-sided significance tests. For the primary comparisons of MED versus CABG in H1 and CABG versus CABG with SVR in H2, the log-rank test will be used, adjusting for the stratum in which the patients were enrolled.[10] Cumulative event rates will be calculated according to the Kaplan–Meier method.[11] Event (or cen-

TABLE 2. STICH trial entry criteria

Inclusion criteria*
- Men
- Women not of childbearing potential
- Age ≥18 y
- LVEF ≤0.35 measured by means of contrast magnetic resonance ventriculography, gated SPECT ventriculography, echocardiography, or contrast ventriculography within 3 mo of trial entry
- CAD suitable for revascularization

Exclusion criteria†
- Failure to provide informed consent
- Aortic valvular heart disease indicating need for aortic valve repair or replacement
- Cardiogenic shock (within 72 h of randomization) defined by need for IABP support or requirement of intravenous inotropic support
- Plan for PCI of CAD
- Recent acute MI judged to be an important cause of LV dysfunction
- History of >1 prior CABG
- Noncardiac illness with a life expectancy of <3 y
- Noncardiac illness imposing substantial operative mortality
- Conditions/circumstances likely to lead to poor treatment adherence (eg, history of poor compliance, alcohol or drug dependency, psychiatric illness, and no fixed abode)
- Prior heart, kidney, liver, or lung transplantation
- Current participation in another clinical trial in which the patient is taking an investigational drug or receiving an investigational medical device

MED therapy eligibility criteria
- Absence of left main CAD defined by intraluminal stenosis ≥50%
- Absence of Canadian Class III angina or greater (angina markedly limiting ordinary activity)

SVR eligibility criterion
- Dominant akinesia or dyskinesia of anterior LV wall amenable to SVR

STICH, Surgical Treatment for Ischemic Heart Failure trial; *LVEF*, left ventricular ejection fraction; *SPECT*, single photon emission computed tomography; *CAD*, coronary artery disease; *IABP*, intra-aortic balloon pump; *PCI*, percutaneous coronary intervention; *MI*, myocardial infarction; *LV*, left ventricular; *CABG*, coronary artery bypass grafting; *MED*, medical therapy; *SVR*, surgical ventricular reconstruction. *Patients might qualify for inclusion in the study. †None of these can exist at randomization.

ACD

soring) times for all patients will be measured from the time of randomization (time zero). Relative risks will be expressed as hazard ratios with associated confidence intervals and will be derived from the Cox proportional hazards model.[12,13] The Cox model will also be used in the assessment of treatment differences and analyses for many of the secondary end points. Interim analyses of the data will be performed and reviewed by an independent Data and Safety Monitoring Board appointed by the NHLBI. Interim treatment comparisons will be monitored with the use of 2-sided, symmetric O'Brien–Fleming boundaries generated with the Lan–DeMets α-spending function approach to group-sequential testing.[14,15]

Study Leadership

The STICH trial is an investigator-initiated, international study funded by the NHLBI of the National Institutes of Health. The STICH Steering Committee is comprised of principal investigators at all enrolling sites. An executive council is empowered by the Steering Committee to make day-to-day decisions (Appendix E1). However, all major executive council decisions are subject to review and approval of the Steering Committee.

Trial operations, site management and monitoring, statistical planning, and data analysis are being coordinated at the Duke Clinical Research Institute of Duke University in Durham, North Carolina. An end point classification committee blindly adjudicates all hospitalizations during follow-up. This committee functions independently of the operational team and is chaired by a cardiovascular specialist without direct access to potential STICH patients. A fully independent Data and Safety Monitoring Board (Appendix E2) has been empowered to review unblinded safety and efficacy data no less than twice yearly by using the prespecified early termination rules described in the previous section.

Results

Enrollment is now complete in both STICH hypotheses. Follow-up will continue until sufficient end points are available to address both hypotheses with at least 90% power. The primary outcome of hypothesis 2 is expected to be reported in 2009. The primary outcome of hypothesis 1 is expected to be reported in 2011.

Discussion

Rationale for Contemporary Evaluation of Survival Benefit Associated With Addition of CABG to MED in Patients With Ischemic Cardiomyopathy

Randomized trials of CABG surgery enrolling 2234 patients between 1971–1979 established the safety of surgical revascularization in patients with preserved LV systolic function and chronic stable angina.[5] Improved survival after CABG compared with that with MED alone was shown for patients with angina and flow-limiting stenoses of the left main coronary artery or multiple coronary arteries, especially in patients with severe stenosis of the proximal left anterior descending coronary artery. The Coronary Artery Surgery Study (CASS) was the only one of these 7 early studies to stratify randomization of the 780 patients enrolled based on LVEF (0.35–0.50 vs >0.50), angiographic extent of CAD (1-, 2-, or 3-vessel stenosis), and presence or absence of angina at the time of enrollment. At the conclusion of 10 years of follow-up, 82 (21%) of 390 patients randomly assigned to receive MED alone had died, and 70 (18%) of 390 patients randomly assigned to receive MED plus CABG had died ($P = .25$).[16] The subgroup of patients with an LVEF of 0.35 to 0.50 was the only stratified subgroup in CASS to show a significant survival difference.[3] Of the 160 patients in CASS who had LVSD, 32 (38%) of the 82 MED-treated patients died, whereas 16 (21%) of the 78 patients who underwent CABG ($P = .01$)

died. However, the 54-patient subset of CASS who had LVSD but no angina did not derive a statistical survival advantage from CABG ($P = .12$).

Since the initial description of the clinical syndrome of ischemic cardiomyopathy more than 3 decades ago,[17] the clinical care of patients with CAD and LVSD has undergone a dramatic evolution. When the last patient was randomized between CABG and MED during the time of CASS enrollment, MED for patients with HF, LVSD, and CAD was limited to digitalis and diuretics, which are medications now known to have a neutral effect on mortality. Current American College of Cardiology/American Heart Association guidelines highlight the major advances in pharmacotherapy and device therapy that have improved the quality of life and survival of patients with CAD, HF, and LVSD.[18] However, the evidence base remains deficient in identifying which, if any, patients with CAD and LVSD should receive revascularization. Although specific clinical problems in this population, such as severe angina, are used to decide on revascularization strategies, the vast majority of patients with ischemic cardiomyopathy have limited or no angina and fall into a gray zone, where clear evidence for adding CABG to MED is either absent or outdated. Thus, divergent views have evolved among clinicians since the reports of the CASS data as to the most appropriate diagnostic and management strategy for patients with ischemic cardiomyopathy. Table E3[18-22] summarizes current guideline recommendations as they relate to the selection of CABG as a treatment option for patients with poor LV function.

The weight of observational data suggests that HF and LVSD remain associated with a higher risk of post-CABG complications and mortality, and although increasing numbers of patients with LVSD and angina are referred to CABG, it might remain underused.[23,24] Of the 24,959 patients screened and entered into the CASS registry from 1975-1979, 751 patients had severe LVSD (as defined by an LVEF <35%), 231 patients underwent CABG, and 420 patients remained on MED.[4] Overall 5-year survival favored MED. However, the subset of patients with an LVEF of less than 26% had a survival advantage demonstrated for the 82 patients who received CABG compared with the 172 patients treated medically ($P = .006$). The CASS registry CABG group had more angina and less severe LVSD than the CABG cohort in the randomized trial. The CASS registry patients undergoing CABG presenting with angina had improved survival free of functional limitation, but patients with predominant HF did not. A large observational series summarized outcomes for 1391 patients with CAD and an LVEF of less than 40% who underwent diagnostic coronary angiography from 1969–1994.[7] After adjustment for baseline differences, the 339 patients who received CABG had a better survival rate than the 1052 patients who received only MED. However, unlike CASS registry patients, this observed survival advantage occurred in all patients, regardless of LVEF and HF status. The perspective that CABG use in patients with LVSD should be confined only to the patient subset with ongoing angina continues to influence treatment guidelines today. Should the STICH trial show that revascularization provides survival benefit beyond that of modern MED, not only will CABG be used more aggressively in patients with LVSD and CAD amenable to CABG, but it will also indicate the need to evaluate for CAD in all patients who present with HF and LVSD.

Rationale for a Prospective Assessment of Myocardial Viability

Viability testing by various modalities is currently used by many clinicians to select patients for surgical intervention. Positron emission tomography has been considered by many to be the gold standard, but high cost and lack of widespread availability has led to limited use.[25] Thallium- or technetium-based nuclear scintigraphy, using one of many rest or stress imaging protocols, has become more widespread and has acceptable sensitivity and specificity.[26] Because it is readily available, dobutamine stress echocardiography to demonstrate augmentation of the contractile response has become the test of choice for assessing tissue viability at many institutions.[27] Although not as widely available, delayed contrast enhancement on cardiovascular magnetic resonance scanning is a reliable method to detect nonviable myocardium.[28] Although guidelines recommend that the presence or absence of viable myocardium can be considered in the decision as to whether revascularization should be recommended,[18-21] the strength of this recommendation varies among the individual guidelines (Table E3). Therefore extensive heterogeneity exists on how clinically available structural and functional imaging is incorporated into treatment decisions for patients with CAD and LVSD.

Viable myocardium in patients with LVSD and CAD appears to predict contractile recovery in dysfunctional myocardial segments, regardless of whether patients receive MED alone or CABG.[29] Although no studies have validated the use of viability testing regardless of the imaging modality in a prospective randomized trial with a survival end point, many retrospective nonrandomized observational series have been published that evaluated the association between the results of viability testing and short-term clinical outcomes. Systematic reviews[30,31] suggest that, when present, myocardial viability is associated with improved short-term (18 month) survival in patients referred to CABG, but conversely, the absence of viability is not necessarily associated with disparate outcomes between medically and surgically treated patients. Unfortunately, a multitude of confounding factors, including the lack of standard

definitions for viability, the heterogeneous nonrandomized populations studied, and the lack of uniform MED received, limit the applicability of these data to current practice. Although the use of viability imaging is predicated on an ability to predict functional recovery, failure to improve LV function is not necessarily associated with a worse clinical outcome.[32] Because CABG in patients with LVSD continues to be associated with substantial operative risk, when and how viability imaging is used to reliably predict long-term outcomes are critical questions that require definitive answers.

Rationale for SVR as an Adjunct to CABG for Patients With Predominant Anterior Akinesia

Surgical reconstruction of akinetic, dyskinetic, or aneurysmal segments might theoretically decrease LV wall stress, myocardial oxygen consumption, and stroke volume while preserving or improving contractile function in the remaining ventricle. In the CASS registry population of LVSD, more than 30% of the patients who underwent CABG underwent concomitant ventricular reconstruction surgery.[4] These early linear plications or resections of dyskinetic scar commonly deformed the LV cavity into a box-like shape and did not consistently improve ventricular performance.[33] Intracavity reconstruction techniques were developed for repairing defects left by aneurysmal resection that reduced LV cavity size but retained a more elliptical configuration of the ventricle.[34] Dor and colleagues[8] advocated the use of SVR not only in patients with dyskinetic scar but also in those with only akinetic myocardial segments. A preserved epicardial covering of myocardial fibrosis might make these akinetic zones appear normal at the time of cardiac operation, but palpable thinning usually can be appreciated in the arrested decompressed heart. Unlike earlier LV aneurysmectomy that removed myocardial scarring or the Batista operation[35] that reduced LV size by means of excision of portions of the LV wall, the objective of the SVR operation is to reshape and decrease the size of the left ventricle by decreasing the circumference of the endocardial scar through an incision in normal epicardium. Myocardial scar is occasionally excised during SVR, but, commonly, no tissue is removed at the time of the operation. The intrinsic scar or an extrinsic patch can be used during closure of the left ventriculotomy to decrease linear wall tension and avoid the restrictive physiology of undersizing the left ventricle.

The RESTORE registry group reported on 1198 patients who underwent SVR at 11 centers, with a 5.1% operative mortality and an 88% 18-month survival rate for all patients.[36] A recent report from the Society of Thoracic Surgery database[37] suggests that SVR is being performed with increasing frequency for the treatment of patients with HF, CAD, and LVSD; however, the perioperative risk might be more substantial. In this 2002–2004 US sample, 731 patients underwent SVR at 141 of 576 reporting centers. The perioperative 30-day outcomes were 9.3% for mortality and 33.5% for any major complication. Use of SVR as an adjunct to CABG for patients with LVSD cannot yet be justified on firm evidence because no reports are available comparing outcomes of CABG and SVR with CABG alone in similar populations. H2 of the STICH trial was designed to address this important question.

Current Status of the STICH Trial

The first patient was randomized into the STICH trial in July 2002. Since then, the STICH Steering Committee has approved 3 protocol amendments to facilitate successful completion of trial enrollment (Appendix E3). Randomization of 1000 planned subjects into H2 was completed in January 2006 and led to the closure of strata B and C to further enrollment. This represents the largest randomized comparison of 2 cardiac surgical strategies. H2 primary end point results are expected to be published in 2009. In June 2006, STICH enrollment into H1 surpassed the CASS study as the largest comparison of cardiac surgical and medical approaches to chronic CAD. H1 completed enrollment in May 2007. Published H1 results are anticipated by 2011.

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APPENDIX E1. Surgical Treatment for Ischemic Heart Failure Executive Council

Study Chair: Jean L. Rouleau, MD
Principal Investigator, Clinical Coordinating Center: Robert H. Jones, MD
Principal Investigator, Data Coordinating Center: Kerry L. Lee, PhD
Director, Global Trial Operations: Eric J. Velazquez, MD
Chair, Core Laboratory Committee: Jae K. Oh, MD
Co-Chair, Surgical Therapy Committee: Robert H. Michler, MD
Co-Chair, Medical Therapy Committee: Christopher M. O'Connor, MD
Program Officer, National Heart, Lung, and Blood Institute: George Sopko, MD

APPENDIX E2. Surgical Treatment for Ischemic Heart Failure trial Data and Safety Monitoring Board

Chair: Sidney Goldstein, MD
Felicia Cohn, MD
Kathryn Davis, PhD
Charles Francis, MD
Mark Hlatky, MD
Scott Rankin, MD
Robert Robbins, MD
Barry Zaret, MD

APPENDIX E3. Summary of Surgical Treatment for Ischemic Heart Failure trial design changes introduced by revisions to the original protocol

	Protocol version 1: January 18, 2002	Protocol version 2: February 24, 2003	Protocol version 3: November 1, 2004	Protocol version 4: May 1, 2006
Entry criteria	Symptomatic HF = NYHA class II in previous 3 mo required	NYHA class I-IV eligible	No further change	No further change
	SVR eligibility: • ESVI $\approx$ 60 mL/m^2 • anterior akinesia = 35% • inferior akinesia absent • right and left circumflex coronary artery graftable	SVR eligibility: • Investigator determined dominant akinesia or dyskinesia of the anterior wall amenable to SVR	No further change	No further change
	LVEF $\approx$ 0.35 measured by CMR, gated SPECT, contrast ventriculography at site or echocardiography core laboratory reading	Echocardiography core laboratory reading requirement dropped; any site reading of LVEF $\approx$ 0.35 regardless of modality before randomization acceptable	No further change	No further change
	Any MI within 30-d exclusion	MI judged to be an important cause of LVSD within 30-d exclusion	No further change	No further change
	Refractory potentially lethal ventricular arrhythmia exclusion	Potentially lethal ventricular arrhythmia exclusion dropped	No further change	No further change
Core laboratory studies	RN stress perfusion study required on strata A and B patients	RN stress perfusion study strongly encouraged but not required	No further change	No further change

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APPENDIX E3. Continued

	Protocol version 1: January 18, 2002	Protocol version 2: February 24, 2003	Protocol version 3: November 1, 2004	Protocol version 4: May 1, 2006
	Baseline RN viability imaging required for strata A and B subjects; DSE performed as ancillary study	—	Baseline RN, DSE, or both viability strongly encouraged for strata A and B subjects	No further change
	Blood sample for NCG studies required of all subjects	—	Blood sample for NCG studies strongly encouraged but not required	No further change
Sample size	Hypothesis 1 sample size 2000 patients	—	Hypothesis 1 sample size reduced	No further change
Frequency of follow-up visits	Follow-up visits required every 4 mo	—	—	Follow-up visits required every 4 mo during first year and then every 6 mo thereafter
Study duration	Follow-up to close December 31, 2008	—	—	Study termination end point driven (400 primary events in hypothesis 1 cohort)

STICH, Surgical Treatment for Ischemic Heart Failure trial; *HF*, heart failure; *NYHA*, New York Heart Association; *SVR*, surgical ventricular reconstruction; *ESVI*, end-systolic volume index; *LVEF*, left ventricular ejection fraction; *CMR*, cardiovascular magnetic resonance; *SPECT*, single photon emission computed tomographic; *MI*, myocardial infarction; *LVSD*, left ventricular systolic dysfunction; *RN*, radionuclide; *DSE*, dobutamine stress echocardiography.

TABLE E1. STICH baseline evaluation studies

Stratum A	Stratum B	Stratum C
All consenting patients		
Echo to Core	Echo to Core	Echo to Core
QOL to Core	QOL to Core	QOL to Core
EuroQOL to Core	EuroQOL to Core	EuroQOL to Core
CMR, gated SPECT, or Echo for LV function	CMR, gated SPECT, or Echo for LV function	CMR, gated SPECT, or Echo for LV function
When feasible		
NCG blood to Core	NCG blood to Core	NCG blood to core
Myocardial viability to Core	Myocardial viability to Core	
Patients able		
6-min walk	6-min walk	6-min walk
Exercise stress	Exercise stress	Exercise stress

STICH, Surgical Treatment for Ischemic Heart Failure trial; *Echo*, Echocardiography; *QOL*, quality of life; *CMR*, cardiovascular magnetic resonance; *SPECT*, single photon emission computed tomography; *LV*, left ventricular; *NCG*, neurohormonal, cytokine, and genetic analyses.

TABLE E2. STICH follow-up evaluation studies

Interval/patient characteristics	Stratum A	Stratum B	Stratum C
4 mo			
All patients	Echo to Core; EuroQOL to Core	Echo to Core; EuroQOL to Core; V-gram to Core (CMR, SPECT, or Echo)	Echo to Core; EuroQOL to Core; V-gram to Core (CMR, SPECT, or Echo)
When feasible	NCG blood to Core	NCG blood to Core	NCG blood to Core
Patients able	6-min walk	6-min walk	6-min walk
12 mo			
All patients	EuroQOL to Core	EuroQOL to Core	EuroQOL to Core
Patients able	6-min walk	6-min walk	6-min walk
24 mo			
All patients	Echo to Core; EuroQOL to Core	Echo to Core; EuroQOL to Core; V-gram to Core (CMR, SPECT, or Echo)	Echo to Core; EuroQOL to Core; V-gram to Core (CMR, SPECT, or Echo)
Patients able	6-min walk; exercise stress	6-min walk; exercise stress	6-min walk; exercise stress
36 mo			
All patients	EuroQOL to Core	EuroQOL to Core	EuroQOL to Core
Patients able	6-min walk	6-min walk	6-min walk
48 mo			
All patients	EuroQOL to Core	EuroQOL to Core	EuroQOL to Core
Patients able	6-min walk	6-min walk	6-min walk

STICH, Surgical Treatment for Ischemic Heart Failure trial; *Echo*, echocardiography; *QOL*, Quality of life; *V-gram*, ventriculogram; *CMR*, cardiovascular magnetic resonance; *SPECT*, single photon emission computed tomography; *NCG*, neurohormonal, cytokine, and genetic analyses.

TABLE E3. Current recommendations relating to the selection of patients with poor LV function for CABG

Guideline/indication	Classification of recommendation	Level of evidence
ACC/AHA 2004 guideline update for CABG surgery[19]		
CABG should be performed in patients with poor LV function who have significant left main coronary artery stenosis.	Class I	B
CABG should be performed in patients with poor LV function who have left main equivalent: significant (≥70%) stenosis of proximal LAD and proximal left circumflex artery.	Class I	B
CABG should be performed in patients with poor LV function who have proximal LAD stenosis with 2- or 3-vessel disease.	Class I	B
CABG can be performed in patients with poor LV function with significant viable noncontracting, revascularizable myocardium and without the above anatomic patterns.	Class IIa	B
CABG should not be performed in patients with poor LV function without evidence of significant revascularizable myocardium.	Class III	B
ACC/AHA guideline update for the diagnosis and management of chronic HF in the adult[18]		
Physicians should recommend coronary revascularization according to recommended guidelines in patients who have both HF and angina.	Class I	A
Patients with CAD and HF should be treated in accordance with recommended guidelines for chronic stable angina.	Class I	C
Coronary arteriography should be performed in patients presenting with HF who have angina or significant ischemia, unless the patient is not eligible for revascularization of any kind.	Class I	B
Coronary arteriography is reasonable for patients presenting with HF who have known or suspected CAD but do not have angina unless the patient is not eligible for revascularization of any kind.	Class IIa	C
Noninvasive imaging to detect myocardial ischemia and viability is reasonable for patients presenting with HF who have known or suspected CAD but do not have angina, unless the patient is not eligible for revascularization of any kind.	Class IIa	C
Noninvasive imaging might be considered to define the likelihood of CAD in patients with HF and LV dysfunction.	Class IIb	C
ACC/AHA/ASNC 2003 guidelines for the clinical use of cardiac radionuclide imaging[21]		
Predicting improvement in regional and global LV function after revascularization with:		
• Stress/redistribution/reinjection thallium-201, rest-redistribution imaging, perfusion plus PET FDG imaging, resting, sestamibi imaging	Class I	B
• Gated-SPECT sestamibi imaging	Class IIa	B
• Late thallium-201 redistribution after imaging after stress	Class IIb	B
• Dobutamine RNA, postexercise RNA, postnitroglycerin RNA	Class IIb	C
Predicting improvement in HF symptoms after revascularization with:		
• Perfusion plus PET FDG imaging	Class IIa	B
Predicting improvement in natural history after revascularization with:		
• Thallium-201 imaging (rest-redistribution and stress/redistribution/reinjection), perfusion plus PET FDG imaging	Class I	B
ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography[20]		
Exercise or pharmacologic stress echocardiography for the assessment of myocardial viability (hibernating myocardium) for planning revascularization	Class I	Not ranked
ACC/AHA 2002 guideline update for the management of patients with chronic stable angina[22]		
In patients with stable angina, CABG for patients with 3-vessel disease; survival benefit is greater in patients with abnormal LV function.	Class I	A
In patients with stable angina, CABG for patients with 2-vessel disease with significant proximal LAD CAD and either abnormal LV function (EF <50%) or demonstrable ischemia on noninvasive testing	Class I	B

LV, Left ventricular; *CABG*, coronary artery bypass grafting; *ACC*, American College of Cardiology; *AHA*, American Heart Association; *LAD*, left anterior descending coronary artery; *HF*, heart failure; *CAD*, coronary artery disease; *ASNC*, American Society for Nuclear Cardiology; *PET*, positron emission tomography; *FDG*, fluorodeoxyglucose; *SPECT*, single photon emission computed tomography; *RNA*, radionuclide angiography; *ASE*, American Society of Echocardiography; *EF*, ejection fraction.